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Applicant: Jong Soo WOO

Serial No.: 10/762,239

Art Unit: 1615 Filed: January 23, 2004

Examiner: Retford Berko

For: Enteric Coated Formulation of a Benzimidazole

Derivative And Method of Preparation Thereof

**DECLARATION UNDER 37 C.F.R. SECTION 1.132**Commissioner for Patents  
Alexandria, VA 22314-1450

I, Jong Soo WOO, a citizen of Korea, residing at Daelim-Jinheong Apt. #821-105, Daewol-Maeul, 914, Jungia-Dong, Jangan-Ku, Suwon-Shi, Kyunggi-Do, Korea, hereby declares as follows:

1. I am an inventor of the subject matter of the above identified application.
2. My personal particulars are summarized as follows:

**[Education]**

1998. 3 – 2001. 2: Ph.D. (pharmaceutics) College of Pharmacy, Chungnam National University

1996. 3 - 1998. 2: M.S. (Pharmaceutics), College of Pharmacy, Chungnam National University

1986. 3 - 1990. 2: B.S. (Pharmaceutics), College of Pharmacy, Youngnam University

**[Employment]**

1990. 2 - 1992. 1: Researcher, Department of Quality Control, Hanmi Pharm Company

1992. 2 - 1999. 3: Chief Researcher, Pharmaceutical Research Center, Hanmi Pharm Company

1999. 4 - 2003. 12: Team Leader, Pharmaceutical Research Team, Hanmi Pharm Company

2004. 1 – Present : Director, Pharmaceutical Research Center, Hanmi Pharm Company

2003. 1 – Present : Professor, College of Pharmacy, Youngnam University

**[Publications ]**

Jong Soo Woo et al., Enhanced Oral Bioavailability of Paclitaxel by Coadministration of the P-Glycoprotein Inhibitor KR30031. Pharmaceutical Research, 20(1), 24-30, 2003.

Jong Soo Woo et al., HPLC of Acetyl-L-carnitine in Human Plasma by Derivatization with

USSN 10/762,239  
WOO

p-Bromophenacyl Bromide. I: *Liq. Chrom. & Rel. Technol.*, 24(4), 555-563, 2001.

Jong Soo Woo et al., Preparation and Evaluation of Non-crystalline Cefuroxime Axetil Solid Dispersion. I: *Kor. Pharm. Sci.*, 32(2), 73-80, 2002.

Jong Soo Woo et al., Bioequivalence of Hanmi Domperidone Tablets to Motilium-M Tablets (Domperidone Maleate 12.72mg). I: *Pharm. Sci. (C.N. U)*, 17, 96-105, 2002.

Jong Soo Woo et al., Preparation and Evaluation of Bupivacaine Microspheres by a Solvent Evaporation Method (II). *Yakhak Hoeji*, 45(6), 623-633, 2001.

Jong Soo Woo et al., Bioequivalence Study of Acetyl-L-Carnitine Tablets. *The Journal of Applied Pharmacology*, 9(4), 285-290, 2001.

[Patent Applications]

Since 1996, I have filed about 40 patent applications related to cyclosporin and omeprazole in the Patent Offices in the world including Korea, U.S.A., Europe, Japan etc., some of which were issued in Korea (Patent Nos. 150830, 167613, 137696, 183449, 135736, 216623) and in U.S.A. (Patent Nos. 5639474, 5589455, 5603951, 6039981, 6017290) and so on.

3. I am thoroughly familiar with the Office Action dated September 16, 2004, wherein claims 1, 2, 8, 9 and 10 of the present application are rejected under 35 U.S.C. 103(a) as being unpatentable over Lovgren et al (US 4,786,505) in view of Makino et al (US 5,026,560) further in view of Sarett et al (US 3,336,192), or over Lovgren et al (US 4,786,505) in view of Chen et al (US 6,726,927) further in view of Pierre et al (US 3,324,102).

4. Under my direction and control, a series of accelerated stability tests were conducted for i) comparison of omeprazole formulation using HP-50 and HP-55; and ii) comparison of pantoprazole formulation using HP-50 and HP-55.

**(1) Preparation of Test Samples**

Fifteen core tablets per sample having the ingredients as shown in the following Table 1 were prepared in accordance with the same procedure as Example 1 of the present specification.

USSN 10/762,239  
WOO

Table 1. Composition for core tablets

Ingredients (mg)	Sample 1	Sample 2	Sample 3	Sample 4
Omeprazole-cholestyramine complex	40	40	-	-
Pantoprazole-cholestyramine complex	-	-	40	40
Hydroxypropyl cellulose-L	45	45	45	45
Lactose for direct method (Ludipress, BASF)	193	193	193	193
Sodium starch glycolate	21.2	21.2	21.2	21.2
Silicon dioxide	0.8	0.8	0.8	0.8
Magnesium stearate	2	2	2	2

The obtained core tablets were coated in a pan with the coating compositions which have the ingredients as shown in the following Table 2.

Table 2. Coating composition

Ingredients (mg)	Sample 1	Sample 2	Sample 3	Sample 4
Hydroxypropyl methylcellulose phthalate HP-50	40		40	-
Hydroxypropyl methylcellulose phthalate HP-55	-	40	-	40
Myvacet	2	2	2	2
Acetone	360	360	360	360
95% Ethanol	180	180	180	180

## (2) Test Method

Respective samples were kept under accelerated condition [40 °C, relative humidity (RH) of 75%] for six months. Changes of the residual contents according to the lapse of time in samples were compared after 0, 1, 2, 4, and 6 month(s) (the comparative tests of the contents are based on Test Example 2 of the present specification).

Column;  $\mu$ -Bondapak C18

Detection; UV 280 nm

Mobile phase; acetonitrile; phosphate buffer at pH 7.6 = 34:66

Injection volume; 10  $\mu$ l

Flow rate; 1.1 ml/min

USSH 10/762,239  
WOO

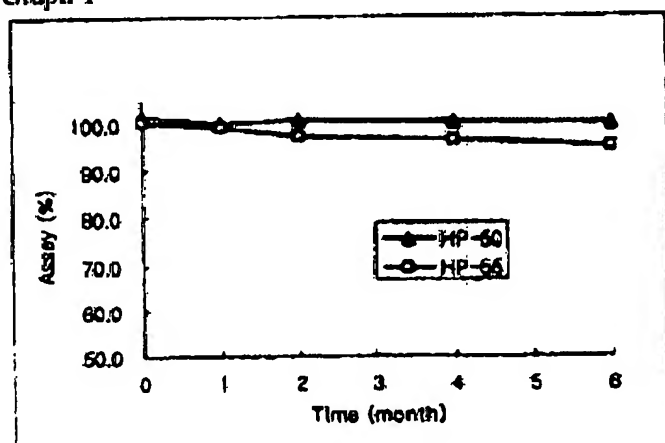
### (3) Test Results (Residual Content)

1) The results of the accelerated stability tests of omeprazole formulations according to the kinds of enteric coating (HP-50, HP-55) are shown in Table 3 and Graph 1 below.

Table 3.

	At First	After 1 month	After 2 months	After 4 Months	After 6 months
Sample 1	101.5	100.2	100.7	100.3	100.1
Sample 2	100.3	99.2	97.5	96.5	95.0

Graph 1



2) The results of the accelerated stability tests of pantoprazole formulation according to the kinds of enteric coating (HP-50, HP-55) are shown in Table 4 and Graph 2 below.

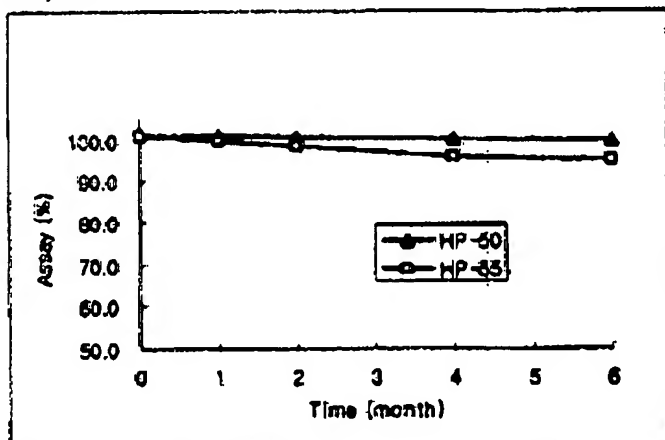
Table 4.

	At First	After 1 month	After 2 months	After 4 Months	After 6 months
Sample 4	101.0	101.2	100.8	100.4	100.1

USSN 10/762,239  
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Sample 5	101.0	100.1	98.5	96.3	95.2
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Graph 2



#### (4) Conclusion

- 1) Accelerated stability test of omeprazole formulation according to the kinds of enteric coating (HP-50, HP-55)

From the results in the above Table 3 and Graph 1, it can be seen that omeprazole formulation coated with HP-50 (Sample 1) has a higher residual content than omeprazole formulation coated with HP-55 (Sample 2) in the accelerated tests for 6 months.

- 2) Accelerated stability test of pantoprazole formulation according to the kinds of enteric coating (HP-50, HP-55)

From the results in the above Table 4 and Graph 2, it can be seen that pantoprazole formulation coated with HP-50 (Sample 3) has a higher residual content than omeprazole formulation coated with HP-55 (Sample 4) in the accelerated tests for 6 months.

5. I hereby declare that all statements made herein to our own knowledge are true and statement made on information and belief are believed to be true; further that these statements

USSN 10/762,239  
WOO

were made with the knowledge that willful false statement and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code that such willful false statement may jeopardize that validity of the application or any patents issuing thereon.

Dated February 11 2005

Signature: J. S. Woo  
Jong Soo WOO

**Shin-Etsu**

2002/05/18 (1/1)

**Certificate of Analysis**



Shin-Etsu Chemical Co., Ltd.  
Naoetsu Plant Quality Assurance Depart.  
28-1 Nishifukushima, Kubiki-mura,  
Nakakubiki-gun, Niigata, Japan

Product Name HPMP  
(Hypermellose Phthalate, NF)  
Grade HP-50  
Nominal Phthalyl Content 24 %  
Viscosity Type 55 cSt  
Lot Number 202114  
Quantity 25kg  
Manufacture Date 2002/02/25  
Expiration Date 2005/02/24  
Analysis Date 2002/02/27  
Issue No. 05120020601086002-1-01  
Remark

This material does not require OVI testing, under the USP-NF <467> stipulation that "... based on knowledge of the manufacturing process and controlled handling and storage... there is no potential for the specific toxic solvents to be present ... If tested, will comply with established standards."  
This product complies with the specifications described in the current NF, EP and JP.  
This product is manufactured in accordance with GMP.

Test Item	Unit	Test Result	Specification
Appearance		White Powder or Granules	
Identification		Conforms	Conforms
Viscosity	cSt	57.8	44 - 86
Water	%	0.8	6.0 Max.
Residue on Ignition	%	0.02	0.20 Max.
Chloride	%	Not more than 0.07	Not more than 0.07
Heavy Metals	%	Not more than 0.001	Not more than 0.001
Limit of Free Phthalic Acid	%	0.13	1.0 Max.
Phthalyl Content	%	22.7	21.0 - 27.0
Methoxyl Content	%	22.2	20.0 - 24.0
Hydroxypropoxyl Content	%	7.2	6.0 - 10.0

*K. ARAUME*

KIYOSHI ARAUME  
General Manager, Q. A. Dept.

Shin-Etsu No. : 12009105-10-01

Issue:  
Shin-Etsu Chemical Co., Ltd.  
Cellulose Division  
6-1, Ohtemachi 2-chome, Chiyoda-ku, Tokyo, Japan  
TEL 81-3-3246-5261 FAX 81-3-3246-5372

Judgment:  
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Naoetsu Plant Quality Assurance Department  
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**Shin-Etsu**

2002/12/18 (1/1)

## Certificate of Analysis

Shin-Etsu Chemical Co., Ltd.  
 Naoetsu Plant Quality Assurance Department  
 28-1 Nishifukushima, Kubiki-mura,  
 Nakakubiki-gun, Niigata, Japan



Product Name HPMCP  
 (Hydromellose Phthalate, NF)  
 Grade HP-55  
 Nominal Phthalyl Content 31 %  
 Viscosity Type 40 cSt  
 Lot Number 211442  
 Quantity 800kg  
 Manufacture Date 2002/11/30  
 Expiration Date 2005/11/29  
 Analysis Date 2002/12/03  
 Issue No. 05120021201451002-1-01

## Remark

This material does not require OVI testing, under the USP-NF <487> stipulation that "... based on knowledge of the manufacturing process and controlled handling and storage... there is no potential for the specific toxic solvents to be present ... If tested, will comply with established standards."

This product complies with the specifications described in the current NF, EP and JP.

This product is manufactured in accordance with GMP.

Test Item	Unit	Test Result	Specification
Appearance		White Powder or Granules	
Identification		Conforms	Conforms
Viscosity	cSt	42.8	32 - 48
Water	%	1.0	5.0 Max.
Residue on Ignition	%	0.02	0.20 Max.
Chloride	%	Not more than 0.07	Not more than 0.07
Heavy Metals	%	Not more than 0.001	Not more than 0.001
Limit of Free Phthalic Acid	%	0.15	1.0 Max.
Phthalyl Content	%	33.3	27.0 - 35.0
Methoxyl Content	%	18.4	15.0 - 22.0
Hydroxypropoxyl Content	%	6.1	5.0 - 8.0

KIYOSHI ARAUME  
 General Manager, Q. A. Dept.

Shin-Etsu No. : 12027635-10-01

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